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Original Article

Acral melanoma: The role of ultraviolet radiation and physical trauma in the pathogenesis of a rare malignancy. systematic review

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ABSTRACT

Melanoma is a malignant neoplasm originating from melanocytes, accounting for a small proportion of skin cancers but responsible for the majority of skin cancer-related deaths. Acral melanoma (AM), affecting the palms, soles, and nail apparatus, exhibits distinct epidemiological, clinical, and molecular features compared with other melanoma subtypes. Trauma and mechanical stress have been implicated in the development of AM, particularly in subungual melanoma, potentially via inflammation, telomere shortening, genomic instability, and modulation of the tumor microenvironment. Ultraviolet (UV) radiation, a well-established risk factor for cutaneous melanoma, appears to play a limited role in AM, although UV-induced mutations may occasionally occur in subungual lesions. Understanding the interplay between trauma, molecular alterations, and the tumor microenvironment is critical for improving early diagnosis, prognostication, and therapeutic strategies in acral melanoma.

Key words: Acral melanoma, Subungual melanoma, Ultraviolet Trauma

INTRODUCTION

Melanoma

Melanoma is a relatively uncommon cutaneous malignancy arising from melanocytes, the melanin-producing cells derived from neural crest stem cells that are responsible for skin and hair pigmentation, accounting for approximately 20% of all skin cancer cases [1,2]. Melanin provides a physiological protective function by limiting DNA damage from ultraviolet (UV) radiation, but it is also crucial for the oncogenic transformation of melanocytes [3,4]. Melanocytes are located in the basal layer of the epidermis and are also found on mucosal surfaces, as well as in the eyes, ears, and meninges [5]. Most melanomas arise *de novo*, while only a small subset develops through a linear progression from benign nevi, via atypical nevi, to melanoma [6,7]. A high number of nevi shows a positive correlation with the risk of melanoma, although Cengiz et al. did not confirm this association in their studied Turkish population. The authors attributed this discrepancy from global reports to the darker skin types predominant in their cohort, mainly Fitzpatrick types 4 and 5 [8]. Although melanoma represents only around 1% of all skin cancer cases, it accounts for nearly 80% of deaths from skin cancer and approximately 2% of all cancer-related deaths, highlighting its disproportionate lethality [1,9].

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Melanomas are most commonly classified according to histopathological features or anatomical location. Histopathologically, the main subtypes include nodular melanoma (NM), superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), acral lentiginous melanoma (ALM), desmoplastic melanoma, and amelanotic melanoma [10]. In the early stages, the tumor typically spreads radially along the dermo-epidermal junction. Over time, as specific genetic alterations accumulate, the growth pattern shifts to a vertical phase, which drives its invasiveness and metastatic potential [11].

Melanoma remains a significant public health concern due to persistently delayed diagnoses and a steadily increasing global incidence. In 2020, more than 324,000 new cases and approximately 57,000 deaths were reported worldwide. Given current trends, projections for 2040 estimate around 510,000 new cases and 96,000 deaths. Men are affected significantly more often, with an incidence rate of 3.8 per 100,000 and a mortality rate of 0.7 per 100,000. For comparison, in women the incidence rate is 3.0 per 100,000, and the mortality rate is 0.4 per 100,000 [12]. Among the established prognostic factors for overall survival are tumor thickness, pathological stage, presence of ulceration, age at diagnosis, sex, and sentinel lymph node biopsy status [10].

Acral Melanoma

Acral melanoma, occurring on the palms, soles, and within the nail apparatus, is a rare subtype of melanoma and accounts for approximately 1–3% of all cases in USA and Europe [1,9,13,14] and 8% in a single cohort study including patients of Middle Eastern descent [2].

However, in Asia, South America, and Africa, it is the most common melanoma subtype, with an incidence of 40–71%. In 60% of patients, it is diagnosed at stage III or higher [14]. Cases of AM are observed almost exclusively in older individuals, and advanced age, along with increased Breslow thickness and the presence of lesion ulceration, constitutes one of the most significant factors associated with poor prognosis [15,16]. Weiss et al. demonstrated that the characteristic localization of acral melanoma to glabrous skin, specifically the palmar surfaces of the hands and plantar surfaces of the feet, is linked to positional identity programs unique to acral melanocytes and to a HOX13 regulated transcriptional state [17]. These factors confer an increased predisposition to the development of distinct melanoma subtypes in these anatomical regions.

Subungual melanoma is a very rare subtype, accounting for approximately 7–30% of acral melanoma cases [18-20], and about 25–33% of these tumors present as amelanotic lesions [18,19]. Given their distinct biological characteristics, melanomas of the nail unit are now recommended to be classified as a separate melanoma subtype [21]. In approximately two-thirds of cases, the clinical presentation consists of longitudinal melanonychia, a nonspecific finding that often leads to delayed diagnosis. In some patients, the tumor may present solely as an indurated plaque or nail dystrophy, further complicating timely and accurate diagnosis [22,23]. The primary site of tumor origin is the nail matrix, with less frequent involvement of the nail bed and periungual epidermis [21]. Subungual melanoma, similar to acral melanoma, occurs more commonly in individuals with darker skin types, particularly Asians and Africans. However, the amelanotic variant is observed predominantly in Caucasian patients and shows a higher incidence among women [22].

Acral melanoma shows a particularly high incidence (39.2%) and, simultaneously, the lowest survival rate among Black patients, irrespective of disease stage at diagnosis [18]. In other populations, the proportion of AM among all melanoma cases is reported as follows: 23.1% in Pacific Islanders and Asians, 9.3% in White Latinos, and 1% in non-Latino Whites. It has been further estimated that in Taiwan, China, Japan, Singapore, Korea, and Hong Kong, this proportion may reach up to 58%, and in the Republic of South Africa even as high as 65% [13,24]. Moreover, more advanced disease stages at the time of diagnosis are disproportionately observed among patients of Black, Hispanic, and Asian descent [25]. When evaluating the higher mortality associated with acral melanoma, it is important to consider its greater prevalence among non-Caucasian populations, many of whom reside in developing countries, where limited access to healthcare services, advanced treatment options, and lower levels of education and socioeconomic status may contribute to delayed diagnosis and worse outcomes [11,25,26].

Accurate diagnosis of a tumor is challenging because its clinical presentation can be difficult to distinguish from benign lesions, such as nevi, warts, hematomas, ulcers, or fungal infections of the skin and nails [11]. An even greater diagnostic challenge is the recognition of amelanotic acral melanoma, which lacks the most characteristic feature of these tumors—the dark

pigmentation [27]. On the feet and hands, the tumor may present as a symmetrical, uniform black or dark-brown macule, and in more advanced stages as a nodule or an ulcerative lesion. In the subungual region, it often manifests as a dark longitudinal streak [21,24].

The classical ABCDE criteria used in melanoma diagnostics are less applicable to the identification of acral melanoma due to its distinct clinical presentation. Consequently, the CUBED acronym (Table 1) has been proposed as a more suitable tool for evaluating lesions in acral locations, along with a modified ABCDEF acronym (Table 2) specifically designed for lesions involving the nail unit [24,28].

Acral melanoma (AM) exhibits a molecular profile that is markedly distinct from that of other melanoma subtypes. These differences include a higher frequency of mutations in the KIT, NF1, and PTEN genes, frequent TP53 inactivation, alterations in TERT, and increased copy numbers of CDK4 and CCND1, together with a lower prevalence of BRAF and NRAS mutations that are characteristic of non-acral melanomas [20,29]. The high heterogeneity of molecular alterations observed in acral melanoma, encompassing single nucleotide variants (SNVs), copy number variations (CNVs), structural variants (SVs), and distinct transcriptomic profiles, presents a significant challenge for contemporary medicine in terms of therapeutic selection [30]. Targeted therapies, including BRAF and KIT inhibitors, as well as immune checkpoint inhibitors, which have substantially improved outcomes in cutaneous melanoma and reduced reliance on surgery, demonstrate limited efficacy in acral melanoma [30,31]. Smith et al. suggested that therapeutic efficacy in acral melanoma may be enhanced by agents that modulate the tumor microenvironment, identifying lenvatinib as a promising candidate with potentially high clinical benefit [30].

Table 1: CUBED acronym [28]

C	Colored
U	Uncertain diagnosis
B	Bleeding lesions
E	Enlarged
D	Deteriorate with delayed healing

Table 2: ABCDEF acronym [28]

A	Age: 20-90 years: African American, Native American; Asian
B	A band of brown or black pigmentation on the nail wider than 3 mm or with irregular, variegated borders
C	Change in the nail band or no change of the nail appearance despite appropriate treatment.
D	Digit involved (the thumb, big toe, index finger, single digit)
E	Brown or black pigmentation extending toward the nail base or sides
F	A personal or family history of melanoma or atypical moles

For the preparation of this manuscript, a comprehensive literature review was conducted focusing on melanoma, acral melanoma, and the influence of ultraviolet radiation and physical trauma on the development of acral melanoma. Electronic databases including PubMed, Web of Science, and Google Scholar were systematically searched, with particular emphasis on studies published over the past twenty-five years. The search strategy involved combinations of the following keywords: melanoma, acral melanoma, hand melanoma, foot melanoma, subungual melanoma, ultraviolet radiation, mechanical stress, trauma, and injury. The identified records were initially screened based on their abstracts, after which the full texts of selected articles were reviewed. Studies providing relevant and substantive information were included in the final analysis.

DISCUSSION

Trauma and Mechanical Stress in Acral Melanoma

Injuries and physical stress are integral components of human activity, particularly among individuals engaged in occupations characterized by manual labor or repetitive tasks, such as those in the agricultural sector [32]. Numerous studies have suggested an association between physical or mechanical stress and the development of acral melanoma at sites of primary injury or mechanical compression [9,33-37].

In a study of 313 Korean patients with acral melanoma, injury, maceration, chronic friction, and repeated rubbing were identified as significant contributing factors in the development of this malignancy, as evidenced by its higher prevalence in anatomical sites most prone to trauma. The most common location (67.8%) was the foot, particularly its peripheral regions, including the heel and forefoot, followed by the nails (27.5%), with the thumb being the most frequently affected digit [32]. Due to the limited amount of soft tissue in the distal parts of the body, treatment of neoplastic lesions in these locations often involves the need for amputation of a portion of the limb, such as the toes [38,39]. The most commonly reported types of trauma associated with tumor development are

lacerations and puncture wounds. Moreover, tumors that developed at the site of the initial injury typically presented with a more advanced pathological stage at the time of diagnosis and more frequently manifested clinically as ulcerated lesions [33].

Some authors suggest that trauma constitutes a significant risk factor for poorer prognosis in acral melanoma and is associated with up to a fivefold increase in melanoma-related mortality [9,33]. Conversely, other investigations have failed to demonstrate a statistically significant relationship between trauma and the development of limb melanomas, leaving this issue a matter of ongoing debate [40-44]. Notably, a positive association between trauma and the risk of developing acral melanoma has been reported primarily in studies from Asian countries, whereas data from the United States have not demonstrated a significant relationship [16].

Among Chinese patients, a higher frequency of trauma-associated acral melanoma has been observed in men with low or intermediate levels of education and in lesions involving the right side of the body. This phenomenon is most commonly explained by the distribution of social roles in many Asian countries, where men, particularly those without higher education, often work in the agricultural or fisheries sectors, which involve substantial physical workload and an increased risk of injury [33].

Other Trauma-Related Factors

The development of malignancy in vulnerable areas of the body may be influenced not only by mechanical stress or physical trauma but also by other factors. The literature describes cases in which squamous cell carcinoma, basal cell carcinoma, and melanoma have arisen from burn scars. Malignant transformation is estimated to occur in up to 2% of post-burn lesions, typically developing several decades after the initial injury. The molecular basis of these transformations has been attributed to an immunologically altered microenvironment and the recurrence of burn injuries [17].

It has been observed that deliberate and controlled human activities resulting in cutaneous trauma, such as tattooing, dermabrasion, and the surgical removal of benign melanocytic nevi, may be associated with the subsequent development of melanoma. Reports in the literature describe melanomas arising in tattooed skin, acquired melanocytic nevi showing post-dermabrasion atypia resembling melanoma in situ, and remnants of previously excised nevi identified within melanomas developing at the original nevus site, suggesting a possible non-causal association with cosmetic and/or medical interventions [45].

Subungual Melanoma: A Trauma-Associated Subtype

Trauma may play a particularly important role in the initiation of tumorigenesis in subungual melanoma [22,32,46,47]. In this patient population, a history of prior injury has been reported in 23–44% of cases [22]. Among patients diagnosed with nail melanoma, the most common location on the hands was the thumb (58%), whereas on the feet it was the hallux (86%) [48]. The higher incidence of tumors in these areas may be explained not only by their increased susceptibility to trauma but also by the relatively larger surface area of the nail matrix [16].

Molecular and Cellular Mechanisms of Trauma-Induced Acral Melanoma

The precise pathogenic mechanism of trauma-induced acral melanoma remains unclear. It is hypothesized that the process is associated with inflammation and immune responses at irritated sites, as well as with repeated activation of the cell cycle, which in turn leads to telomere shortening and increased TERT expression [32]. The immune response, involving macrophages, dendritic cells, neutrophils, monocytes, mesenchymal stromal cells, and the signaling molecules they secrete (cytokines, chemokines), orchestrates a series of changes in the area of injury [22]. Following the initial local inflammatory response, a healing phase occurs, during which the damaged tissues are repaired and remodeled. These processes can have systemic consequences in the form of post-traumatic immunosuppression, which may be further complicated by infection at the site of injury [22].

Proposed molecular mechanisms underlying the development of acral melanoma in body areas subjected to physical stress involve chromothripsis and chromosomal aberrations within “tyfonas” [13]. Chromothripsis is a genomic event characterized by the fragmentation of one or more chromosomes, followed by the disordered reassembly of the resulting segments. It may arise from breakage–fusion–bridge cycles involving dicentric chromosomes, which form when chromatids with telomeres shortened during a “telomere crisis”

fuse. TERT promoter mutations, commonly observed in the early stages of tumor progression, underlie this telomere crisis. Chromothripsis can also result from double-strand DNA breaks caused by mechanical stress [20]. This phenomenon appears to occur at an early stage of acral melanoma development, before point mutations arise, which is supported by the relatively low number of point mutations detected in the amplified CCND1 regions [13].

Tyfonas are large amplicons characterized by numerous junction copy number (JCN) connections and fold-back inversions. They are associated with fusions of protein-coding genes and breakend hypermutations [49]. Tyfonas frequently involve the amplification of oncogenes such as MDM2 and CDK4 and are particularly common in dedifferentiated liposarcoma (80%), acral melanoma (40%), and certain breast cancers, whereas in cutaneous melanomas, they are observed in only about 2% of cases [13, 49].

Immune cells, along with the cytokines they secrete, may also contribute to the development of trauma-induced acral melanoma through modification of the microenvironment at the injury site. Tumor associated neutrophils (TANs), identified in cutaneous melanoma, promote tumor progression by stimulating angiogenesis and inhibiting the antitumor activity of T lymphocytes. In Chinese patients with trauma associated acral melanoma, a higher number of M2 macrophages was observed at the tumor–normal tissue interface compared with patients with acral melanoma without trauma, which correlated with poorer prognosis [33].

Nuclear envelope ruptures and micronuclei damage are commonly observed in plantar melanoma cells. These events result not from direct injury but from mechanical stress on the foot associated with activities such as standing and walking. YAP, a mechanosensitive transcriptional cofactor activated in response to mechanical stress, plays a primary role in nuclear envelope damage. The Hippo signaling pathway, which represses YAP, also contributes significantly to this process. Nuclear membrane and micronuclear damage not only cause DNA lesions but also activate the cGAS–STING pathway, which in cancer cells promotes tumor progression and metastasis [50]. Mechanical pressure on melanocytes may additionally disrupt intercellular communication, damage other subcellular structures, modulate melanoblast differentiation, increase extracellular matrix stiffness, and induce upregulation of the protooncogene cfos [45].

Studies investigating the association between trauma and the risk of developing acral melanoma are predominantly retrospective. Therefore, interpretation of these results must take into account the influence of recall bias, as well as the increased likelihood that patients with a history of injury will seek medical attention, thereby raising the probability of tumor detection [21, 32]. Interestingly, previous damage to the affected body part may reduce oncological vigilance, as observed abnormalities are often attributed to prolonged or improper healing of the initial injury [22].

UV Radiation and Acral Melanoma

Ultraviolet radiation is a form of electromagnetic radiation naturally emitted by the sun and is conventionally divided into UV-A (320–400 nm), UV-B (280–320 nm), and UV-C (100–280 nm). However, only UV-A and the portion of UV-B above 300 nm reach the Earth's surface [51]. Artificial sources of ultraviolet radiation have been present in the human environment for decades. They are most commonly used in the beauty industry, such as in nail lamps or tanning beds, in medicine for phototherapy treatments, and in industry, for example during electric arc welding [52-54].

A clear association between the occurrence of skin melanoma and UV radiation has been demonstrated primarily in individuals with fair skin. Data on people with darker skin types (Fitzpatrick II–IV) are less conclusive, suggesting that other carcinogenic factors may play a greater role [11]. The mutagenic effects of ultraviolet radiation are well documented and are mainly associated with the formation of cyclobutane-type pyrimidine dimers. UV-A penetrates efficiently into the dermis and primarily induces oxidative stress, whereas UVB is mostly absorbed within the epidermis, with only a small fraction reaching the dermis [52]. UV-B is the main contributor to direct DNA damage, including mutations in the TP53 gene, and to photoaging of the skin [52,54]. Ultraviolet radiation also impairs the immune response by damaging Langerhans cells, the principal antigen-presenting cells in the skin, and by stimulating the secretion of immunosuppressive cytokines such as TNF-α [3].

UV radiation has long been recognized as a risk factor for cutaneous melanoma, particularly in cases of intermittent exposure or sunburn; however, its role in the initiation of acral melanoma is less clear [11]. The global consensus is that acral melanoma is not

related to UV exposure, as previous studies show that only 10% of patients with this cancer report a history of excessive UV exposure, and a dominant UV-related mutational profile is observed in only 9% of acral melanomas [14,55].

According to the WHO 2018 classification, acral melanoma, together with Spitz melanoma, melanoma in congenital nevus, melanoma in blue nevus, uveal melanoma, and mucosal melanomas, falls into the *low or no UV/CSD* (CSD-cumulative sun damage) category (Table 3) [56]. It infrequently harbors mutations in BRAF, NRAS, and NF1 (triple wild-type), whereas pathogenic alterations in KIT, SF3B1, CCND1, and CDK4 constitute the more prominent molecular drivers of its tumorigenesis [57]. Given that BRAF and NRAS mutations may be induced by ultraviolet radiation, their lower prevalence in acral melanoma is not unexpected [58]. Similar genetic alterations are observed in mucosal melanoma, further supporting the biological distinction of these two melanoma subtypes from cutaneous melanomas arising at UV-exposed sites [57]. Both types also exhibit chromosomal aberrations more frequently than cutaneous melanomas [24,59]. Within the group of acral melanomas, subungual melanomas show the highest burden of genetic mutations, including those associated with UV radiation [13].

Genomic and methylomic analyses of cutaneous and acral melanomas revealed the presence of UV signature mutations in both groups. As expected, the frequency of these mutations was significantly lower in acral melanomas, detected in only 19% of cases compared with 81.5% of cutaneous melanomas [60].

Table 3: The WHO 2018 classification of melanoma (according to pathways) [56]

Pathway number	Relationship with sun exposure/damage	Subtype
1.	Melanomas developing in sun-exposed skin.	*Low-CSD[1] melanoma/superficial spreading melanoma*
2.		*High-CSD[1] melanoma (including lentigo maligna melanoma and high-CSD[1] nodular melanoma)*
3.		*Desmoplastic melanoma*
4.	Melanomas developing in sun-protected skin or without a known etiological association with UV radiation exposure.	*Malignant Spitz tumor (Spitz melanoma)*
5.		*Acral melanoma (including nodular melanoma in acral skin)*
6.		*Mucosal melanoma*
7.		*Melanoma arising in congenital nevus*
8.		*Melanoma arising in blue nevus*
9.		*Uveal melanoma*

[1]CSD-cumulative sun damage

Acral melanomas exhibit fewer mutational signatures associated with UV exposure and fewer point mutations, whereas a higher number of structural genomic alterations is observed [61]. Notably, Wang et al. reported UV signatures in *in situ* lesions, whereas they were nearly absent in more advanced stages of progression. This suggests that UV exposure may not act as an initiating factor in acral melanoma but could influence the tumor genome after malignant growth has begun. For instance, cancer cells may migrate from the primary site to UV-exposed areas, where they are subsequently affected by UV-induced genomic alterations [62]. Additionally, it was observed that the DNA methylome of cutaneous melanomas lacking UV mutations more closely resembles that of acral melanomas than that of UV-mutated cutaneous melanomas. This pattern is reflected in survival analyses: patients with cutaneous melanoma without UV mutations have poorer outcomes compared with those harboring UV-mutated tumors, with survival more closely approximating that of patients diagnosed with acral melanoma [60].

UV radiation does not appear to influence the risk of developing nail melanoma. In an experimental study evaluating UV penetration through the nail plate, it was demonstrated that UV-B radiation is almost completely blocked by the thick keratin layer, while UV-A radiation penetrates at an average of only 1.65% [21]. The dorsal hand skin also exhibits higher resistance and photoadaptation to UV radiation compared with the skin of other body areas, such as the face, abdomen, or chest, and inducing erythema in this region requires exposure to a UV dose up to four times higher [52]. Nevertheless, Rawson et al. found that in acral melanoma cases, UV-related mutations, if detected, occurred more frequently in subungual melanomas. These observations suggest that although the nail plate and acral skin are highly resistant to ultraviolet radiation, their protective effect may be inadequate [63].

The rising frequency of UV lamp use in nail cosmetic procedures has drawn attention from the medical community regarding their potential to induce skin cancers. However, comparative studies have concluded that these lamps do not pose a significantly higher risk than natural sun exposure and may present a lower hazard than narrowband UVB (NBUVB) therapy [52,53]. Despite the relatively low carcinogenic risk associated with cosmetic procedures involving nail-curing lamps, the use of protective measures, such

as SPF >30 sunscreens or specialized UV-blocking gloves, is nevertheless recommended [52]. However, the assessment of any potential increase in risk, even if minimal, has been evaluated primarily in the context of squamous cell carcinoma and basal cell carcinoma rather than melanoma [52,53].

CONCLUSION

Acral melanoma (AM) differs from other melanoma subtypes in terms of epidemiology, clinical presentation, and molecular profile, often leading to delayed diagnosis and poorer prognosis. The incidence and outcomes of AM vary significantly among racial and ethnic groups, with higher prevalence and lower survival rates observed in Asian, African, and Hispanic populations compared with non-Hispanic Whites. Trauma and mechanical stress may play a significant role in tumor initiation and progression, particularly in subungual melanoma, through modulation of the immune response, genomic instability, and changes in the tumor microenvironment. Ultraviolet radiation appears to have a limited role in the pathogenesis of AM, although its mutagenic effects may influence tumor development in selected cases. Early recognition of AM requires heightened awareness of atypical presentations, especially in acral and subungual locations, and the use of dedicated diagnostic criteria such as CUBED or the modified ABCDEF system. Future therapeutic strategies may benefit from targeting the tumor microenvironment and trauma-associated immune changes, potentially improving outcomes for patients with AM.

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